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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,651	08/27/2001	Tatsuji Seki	9150-0009.10	1049

109 7590 09/22/2004

THE DOW CHEMICAL COMPANY
INTELLECTUAL PROPERTY SECTION
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EXAMINER	
KRUSE, DAVID H	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,651	SEKI ET AL.	
	Examiner	Art Unit	
	David H Kruse	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 15-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 15-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/22/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Inventorship

1. In view of the papers filed 8 October 2003, the inventorship in this nonprovisional application has been changed by the deletion of Toshiomi Yoshida pursuant to 37 C.F.R. § 1.48(b).

In view of this acknowledgement of change of inventorship, Applicant should request a corrected filing receipt to show the change in inventorship.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 22 June 2004, the information disclosure statement is being considered by the examiner. Reference DE 19754622 has been crossed out because no translation has been submitted, and Applicant acknowledges that US Patent 6,653,459 is an English language equivalent.

STATUS OF THE APPLICATION

3. This Office action is in response to the Amendment and Remarks filed 22 June 2004.

4. The objection to the Abstract is withdrawn.

5. Applicant's correction of the claim of priority is noted, but the Examiner suggests inserting the phrase -- published in English -- after the PCT application information to clearly establish the date of priority under 35 U.S.C. § 371.

6. Those rejections or objections not specifically addressed in this Office action are withdrawn in view of Applicant's amendments to the claims or to Applicant's arguments.

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

8. Claims 1-7, 9,10, 12 remain rejected and claims 15-24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is repeated for the reason of record as set forth in the last Office action mailed 22 December 2003. Applicant's arguments filed 22 June 2004 have been fully considered but they are not persuasive.

The issue of the limitation "human-type sugar chain" and the limitation "mammalian-type" as directed to a sugar chain remains, and render claims 1-7, 12, 23 and 24 indefinite. Applicant argues that the terms "having a human-type sugar chain" are defined on page 12, lines 7-22, and because Applicants invention is intended to encompass all such sugar chains made in a transformed plant, limiting this term would exclude intended glycoproteins (page 12 of the Remarks). This argument is not found to be persuasive because the specification at page 12 states "In this specification, "human-type sugar chain" refers to a sugar chain with a galactose residue linked to a N-acetylglucosamine residue", yet this statement does not state the metes and bounds of the invention. The specification also states that in the present invention the glycoprotein can contain neither fucose nor xylose (page 6, lines 30-31), yet the instant claims provides no method steps that produce this required structure, hence the metes and bounds of the claimed invention are unclear.

Claims 4-7 are indefinite because there are no positive method steps recited in either the instant claims or in claim 1, upon which they depend, the produce the claimed structure. Hence, the metes and bounds of the claims are unclear.

Claim 8 is indefinite because it is unclear what the plant is transformed with, it is unclear if the plant cell inherently comprising a sugar chain adding mechanism or if such mechanism is introduced.

At claim 9, line 5, the limitation "which can improve the performance of the first enzyme" renders the claim indefinite because it is unclear what the metes and bounds of "improve" are. At claim 10, it is unclear how the listed "second enzyme" improve the performance of the first enzyme, as the appear to modify the sugar chain, and not the first enzyme. Hence, the metes and bounds of the claims are unclear. Applicant states that Applicant believes this limitation to be clearer in meaning than "enhance" (page 13 of the Remarks). This is not found to be persuasive, the new limitation is found to be just as indefinite as that which it replaces.

Claim 15 is indefinite because the claim recites the limitation "selected from one or more of" at line 5, while at lines 4-5 recited "a gene encoding an exogenous glycoprotein" which appears to be a narrow limitation. In addition, it is unclear how the "glycoprotein produced has no fucose or xylose linked to one or more of the core sugar chain" because there is no positive method steps that would produce this function.

At claim 16, lines 2-3 , the limitation "capable of enhancing the efficiency" renders the claim indefinite because it is unclear what the metes and bounds of this limitation are. At claim 17, the list of "second enzymes" appear to modify the "sugar chain" an do

not enhance the efficiency of the glycosyl transferase enzyme. Hence the metes and bounds of the claimed invention are unclear.

At claims 18-20, line 1, "the exogenous glycoprotein" lacks proper antecedent basis in claim 15.

At claims 21 and 22, the limitation "derived from" render the claims indefinite because it is unclear what the metes and bounds of "derived" are. The Examiner suggest that "derived" be deleted from the instant limitation. Claim 22 uses an improper Markush format and should use the conjunction "and" at line 3.

9. Claims 1-12 remain rejected and claims 15-24 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is repeated for the reason of record as set forth in the last Office action mailed 22 December 2003. Applicant's arguments filed 22 June 2004 have been fully considered but they are not persuasive.

Applicant's arguments on pages 14-17 appear to be directed to the rejection under 35 USC 112, first paragraph, for enablement, and not for written description specifically, to which the instant rejection is directed. The Examiner will attempt to address Applicant's arguments as they relate to the instant rejection.

Applicant argues that it is not critical that the sequences of the resulting plant produced glycoprotein be identical to that made in a human or mammalian system, but

rather that the sequences are as close as possible so that the plant produced glycoprotein function the same as and preferably as well and efficiently as the human or mammalian produced glycoprotein, and that the ultimate use made of the glycoprotein made by a transgenic plant system should be equivalent to that made by a mammalian system (page 15, 4th paragraph of the Remarks). The instant claims have been found to be indefinite for the use of the limitations "mammalian-type" and "human-type" sugar chain as outlined supra, and in the previous Office action. Applicant's arguments are not found to be persuasive because the instant claims are directed to methods using and products comprising polynucleotides encoding a glycosyltransferase enzyme that produces a "mammalian-type" and "human-type" sugar chain on a glycoprotein. The methods of the instant claims appear to require the introduction of multiple, specific transgenes to produce the resulting exogenous glycoprotein. The instant specification only describes how to produce a plant cell that attaches a terminal galactose residue onto a glycoprotein, whether it be endogenous or encodes by an exogenous transgene introduced into said plant cell.

Applicant argues that because the glycoprotein that is being made in plants would be known from another source in order to be an exogenous glycoprotein, the protein made by the plant can be compared for its sugar chain pattern with the known sugar chain pattern, and that the intent is to make a mammalian-type or human-type sugar chain on the plant prepared glycoprotein, the desired outcome can be determined. Applicant further argues that the structure attained may vary somewhat in sequence to attain that result because of expression in plants for example, different

codon optimization patterns, promoters, leader sequence, and thus the function of the present produced biomolecule is correlated to the function of the known biomolecule. Applicant argues that the functional equivalence is what matters rather than the exact same structure (page 16, 1st paragraph of the Remarks). These arguments are not found to be persuasive because the issue at hand is whether Applicant has adequately described "a gene encoding a glycosyltransferase enzyme" required to practice the claimed methods to produce a mammalian-type or human-type sugar chain as broadly claimed. As stated supra, it appears that more than the human galactosyltransferase encoding polynucleotide described in the instant specification would be required to practice the methods as broadly claimed.

Applicant argues that there are well known classes of N-linked glycan enzymes for the claimed glycosylation method in plants (i.e., glycosyltransferase) some of which are IUBMB Nos. EC 2.4.1.101, EC 2.4.1.143, and EC 2.4.1.144, which by their classification transfer mannose residues, and IUBMB No. EC 2.4.1.38, which by their classification transfer galactose and thus all such enzymes do function for their intended use and are well known to one skilled in this art. Applicant argues that because the glycosyltransferase must be able to make a human-type or mammalian-type sugar chain glycoprotein, any enzyme that does not perform its usual function in this method in plants is excluded, and thus this invention is not a function to structure issue, but a function to function issue that is easily confirmed (page 16, 2nd paragraph of the Remarks). Although the instant argument is directed to the scope of enablement, the issue remains as to Applicant's burden to describe the invention such that one of skill in

the art would understand what Applicant was in possession of at the time of filing. Just because other glycosyltransferases were know in the art at the time of filing, Applicant must describe what structural and functional features of the required "gene" are that can be used to practice the claimed invention. Applicant cannot invite experimentation by one of skill in the art.

The addressed arguments appear to be directed to issues of written description. The remainder of the arguments appears to be directed to issues of enablement as will be addressed below.

10. Claims 1-12 remain rejected and claims 15-24 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of manufacturing a glycoprotein in a transgenic plant having terminal galactose residues in the N-glycosylation portion of a glycoprotein comprising transforming said plant with a transgene encoding a mammalian β1,4-galactosyltransferase, and a plant transformed therewith which also comprises a transgene encoding an exogenous glycoprotein, does not reasonably provide enablement for a method of manufacturing a glycoprotein having a human-type sugar chain comprising transforming a plant cell with any gene encoding a glycosyltransferase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is repeated for the reason of record as set forth in the last Office action mailed 22 December 2003. Applicant's arguments filed 22 June 2004 have been fully considered but they are not

persuasive. This rejection addressed those arguments not already addressed supra on pages 14-17 of the response.

Applicants argue that they have demonstrated the presence of galactose on N-linked glycan structures in transformed tobacco cells expressing human β-1,4-galactosyltransferase (hGalT) using Cauliflower mosaic virus (CaMV35S), with horseradish peroxidase (HRP) as the exogenous glycoprotein, and transformation with *Agrobacterium*, and that using this teaching, a person skilled in the art could, without undue experimentation, perform a method of manufacturing a glycoprotein having a mammalian-type sugar chain (page 14 of the Remarks). The issue of indefiniteness of the limitation "mammalian-type" sugar chain is addressed supra. Dinter and Berger, cited in the previous Office action, teach that "human-type sugar chain" or "mammalian-like glycoproteins" encompass a vast variety of combinations of polysaccharides, and that such limitations do not inherently teach the structure of the claimed invention. It is the Examiner's opinion that a teaching of a method of introducing a terminal galactose residue, that is not naturally present in a specific plant, by transforming a plant with a polynucleotide encoding the human β-1,4-galactosyltransferase, does not adequately teach one of skill in the art how to make and use plant that produce mammalian-type sugar chains on an exogenous glycoprotein as broadly claimed.

Applicant argues that by using the teaching in the specification as filed, the skilled person could also, without undue experimentation, produce a range of plant-produced glycoproteins comprising neither fucose nor xylose as required by some of the amended claims, and in a similar manner, a skilled person, without undue

experimentation, could produce a recombinant plant, or portion thereof, that produces mammalian-type glycoproteins (page 14 of the Remarks). This argument is not found to be persuasive for the reasons given supra. As to the issue of "produced glycoproteins comprising neither fucose nor xylose", the instant limitation appears to require the use of a mutant plant that lacks the capacity to introduce a fucose or a xylose onto a glycoprotein. Applicant does not teach how to make and use plants that lack the capacity to introduce a fucose or a xylose onto a glycoprotein as would be required to practice the method of claims 7, 12 and 15-22 as broadly claimed without undue trial and error experimentation. If the ability of a plant to produce glycoproteins comprising neither fucose nor xylose is inherent in the transformed plant, than this limitation does not further limit or define the claimed invention.

Applicants argue that they have subsequently produced data for whole plants that shows similar results for N-linked glycan structures to that obtained for plant cells described in the present application. Applicants argue that these results demonstrate that glycosyltransferase, shown by galactosyltransferase and hGalT, when expressed in mature plants (present Affidavit) or calli (specification), modifies the structure of N-linked glycans in a manner similar to that seen in mammalian systems (page 14 of the Remarks). The Seki and Fujiyama Declaration filed under 37 CFR § 1.132 has been reviewed by the Examiner. The instant argument is not found to be persuasive for the reasons given supra. The Seki and Fujiyama Declaration does not overcome the instant rejection because it does not specifically overcome the issue of scope of enablement of the instant claims. The Seki and Fujiyama Declaration only provides

evidence that a regenerated whole plant produces glycoproteins with terminal galactose residues.

Applicant argues that a later published application (WO 01/29242) has shown that the scope of the present claims is reproducible. Applicant argues that this publication tobacco calli, soybean calli and corn calli were used to illustrate the successful placement of galactose on N-linked glycan structures of a human monoclonal antibody (hMAb) and collagen in biolistic-transformed calli using prolyl 4-hydroxylase (P4H) as the glycosyltransferase, which expressions were driven by the CaMV35S promoter, but no whole plants were used or regenerated. This argument is not found to be persuasive because the disclosure of WO 01/29242 does not provide enablement for the breadth of the claimed invention, it only confirms what Applicant has taught in the instant specification and nothing more.

Applicant argues that because the glycoprotein that is being made in plants would be known from another source in order to be an exogenous glycoprotein then the protein made by the plant can be compared for its sugar chain pattern with the known sugar chain pattern, and the intent is to make a mammalian-type or human-type sugar chain on the plant prepared glycoprotein, the desired outcome can be determined (page 16, 1st paragraph of the Remarks). This argument is irrelevant to the instant rejection. The Examiner does not find the expression of an exogenous glycoprotein in a transgenic plant to lack adequate enablement. The issue is whether Applicant has taught one of skill in the art how to make and use a transgenic plant that produces a mammalian-type glycosylated glycoprotein as broadly claimed.

Applicants argue that they have now shown by other published patents that other such enzymes are effective as exogenous glycosyltransferase enzymes as exemplified in WO 01/29242 (page 16, 3rd paragraph of the Remarks). This argument is not found to be persuasive for the reasons given supra.

Applicant argues that the use of the produced glycoprotein will be based on the selection of the protein to be glycosylated, its use will already be known, and that the desired glycoprotein will have a known utility and been tested from a normal source or made in a microorganism or CHO cells. Applicant argues that this is a new process to manufacture that glycoprotein and have the sugar chain added as close in structure to that already known to maintain the protein activity, folding, binding affinity, and other properties, and that Applicant believes that one skilled in the art will know how to achieve all the features of that product as now claimed (page 17, 3rd paragraph of the Remarks). This argument is not found to be persuasive because the issue is not the use of the product produced by the transformed plant, but how to make and use the transformed plant as broadly claimed.

Claim Rejections - 35 USC § 102

11. Claims 1-7 remain rejected and claims 23 and 24 are rejected under 35 U.S.C. § 102(e) as being anticipated by Umana *et al*, U.S. Patent 6,602,684, issued 5 August 2003, filed 20 August 1999, and claims priority to US Provisional Application 60/082,581, filed 20 April 1998. This rejection is repeated for the reason of record as set forth in the last Office action mailed 22 December 2003. Applicant's arguments filed 22 June 2004 have been fully considered but they are not persuasive.

Applicant argues that Umana *et al* disclose that the preferred host cells (column 1, lines 52-53) and that plant cells, among other host systems, are least desired with the reasons why given (column 1, lines 56-61), and thus this cited patent teaches away from the present invention. This argument is not found to be persuasive because Umana *et al* the reasons given at column 1, lines 56-61, are only illustrative of why one would modify other expression systems, it does not teach away from the instant claims, but discloses why one of skill in the art would modify plant cells to produce therapeutic glycoproteins. The instant rejection remains.

Claim Rejections - 35 USC § 103

12. Claims 8-12 remain rejected and claims 15-22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Umana *et al*, U.S. Patent 6,602,684, issued 5 August 2003, filed 20 August 1999, and claims priority to US Provisional Application 60/082,481, filed 20 April 1998, in view of Hein *et al*, U.S. Patent 5,959,177, filed 3 May 1996. This rejection is repeated for the reason of record as set forth in the last Office action mailed 22 December 2003. Applicant's arguments filed 22 June 2004 have been fully considered but they are not persuasive.

Applicant argues that the critical nature of the choice of the host cell line is discussed by N. Jenkins et al., Nature Biotech. August 1996, copy provided, where the differences in carbohydrate structures are described based on which expression system is selected, the culture conditions used, and the analysis employed for the carbohydrate structure, and that this article shows that shifting from one host cell system to another, even with all the technical differences that would have to be known and adjusted, still

results in carbohydrate differences for both the pattern of sugars attached and in that different structures are formed on the glycoprotein. Thus the choice of a plant cell or whole plant system results in a different glycoprotein prepared from that of a mammalian cell system, and that the glycoprotein made would be different from that obtained by the present claimed invention (page 20, 2nd paragraph of the Remarks). This argument is not found to be persuasive because it appears to argue against the scope of enablement of Applicant's own claims. This reference does not teach away from the instant claims.

Applicant argues that Hein does not teach glycosylation of the antibody other than what the native plant might provide and that no attempt was done to make a mammalian-type or human-type sugar chain as required by the cited patent claims (page 20, 3d paragraph of the Remarks). This argument is not found to be persuasive because Hein teaches that one of ordinary skill in the art can express exogenous glycoproteins in a plant as exemplified by Hein's production of a functional antibody in a plant. It is the teachings of Umana *et al* that teach one of ordinary skill in the art how to introduce a "mammalian-type" glycosylation onto an exogenous antibody expressed in a plant cell.

Applicant argues that combining the teachings from the cited Umana patent with the cited Hein patent is just not technically feasible nor would the carbohydrate residue pattern obtained by either method be similar (page 20, 4th paragraph of the Remarks). This argument is not found to be persuasive because the instant claims do not recite a limitation as to any specific structural feature of the produced glycoprotein other than it

comprises a terminal galactose residue, a function that would be obvious to one of ordinary skill in the art at the time of Applicant's invention.

Applicant argues that because the pathways for glycosylation are so different, the only recourse is to "try" to make it work, and that "this" is not a teaching that would enable one skilled in the plant art to implement the teachings from a mammalian cell system (page 21, 1st paragraph of the Remarks). This argument is not found to be persuasive because Umana motivates one of ordinary skill in the art to use the taught method in a plant cell.

Applicant argues that because the cited Umana patent also teaches that yeasts could be used, but without much guidance as to making that system function, the art shows that changing from a human system to yeast results in significant glycosylation differences as well (page 21, 2nd paragraph of the Remarks). This argument is not found to be persuasive because the references cited are directed to very complex modification of yeast glycosylation pathways, comprising making null mutant, which the neither the instant claims nor the cited prior art teach.

13. Claims 1-12 and 15-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al* (Annual Reports of IC Biotech, Vol. 18, pages 241-247, publicly available 21 August 1998), in view of Umana *et al*, U.S. Patent 6,602,684, issued 5 August 2003, filed 20 August 1999, and claims priority to US Provisional Application 60/082,481, filed 20 April 1998, in view of Hein *et al*, U.S. Patent 5,959,177, filed 3 May 1996

Zhang *et al* teach transforming tobacco with a gene encoding a human β-1,4-galactosyltransferase gene and regenerating a transgenic plant. Zhang *et al* teach that such a plant could be used to produce antibodies or other exogenous proteins with "human-type" glycosylation (see pages 241-242).

The teachings of Umana *et al* and Hein *et al* can be found in the previous Office Action.

It would have been prima facie obvious to one of ordinary skill in the art at the time of Applicant's invention to modify the teachings of Zhang *et al* to express an antibody gene in the tobacco plant as taught by Hein *et al* to produce an exogenous antibody glycoprotein with "human-type" sugar chains. It would have also been obvious to one of ordinary skill in the art to introduce other enzyme encoding genes such as mannosidase as suggested by Umana *et al*. Given the success of expressing human β-1,4-galactosyltransferase in a tobacco plant as taught by Zhang *et al* and expressing antibodies in tobacco as taught by Hein *et al*, one of ordinary skill in the art at the time of Applicant's invention would have had a reasonable expectation of success.

Conclusion

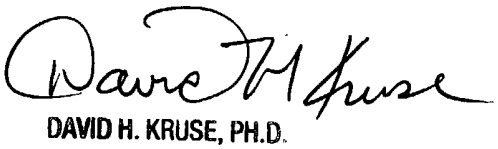
14. This Office action is non-final in view of the new grounds of rejection.

15. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David H. Kruse, Ph.D. whose telephone number is (571) 272-0799. The examiner can normally be reached on Monday to Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy Nelson can be reached at (571) 272-0804. The fax telephone number for this Group is (703) 872-9306 Before Final or (703) 872-9307 After Final.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group Receptionist whose telephone number is (571) 272-0547.



DAVID H. KRUSE, PH.D.
PATENT EXAMINER

David H. Kruse, Ph.D.
20 September 2004

16. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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